I- Initiation of Cardiac Electrical Activity

Automaticity & Rhythmicity of the Heart

- **Automaticity** → ability of the heart to initiate its own contraction independent of external stimuli
- **Rhythmicity** → heart can beat regularly
- Automaticity & rhythmicity are due to spontaneous & regular pacemaker AP
- **Pacemaker cells are present in SA node, AV node & Purkinje fibers:**
  a. **SA node → normal human pacemaker** → fastest rate of AP (105/min)
  b. If the SA node fails, → AV node (60/min) becomes the pacemaker
  c. If the AV node fails, → Purkinje cells (40/min) become the pacemaker → idio-ventricular rhythm
  d. SA node → 60-200 AP/min under various normal conditions
  e. "**Vagal tone**": normally, parasympathetic (vagal) effect on SA node is stronger than sympathetic → ---- SA node rate → normal resting HR = 72 beats/min

Pacemaker potential: 3 phases: phases 4, 0 & 3

Phase 4: Pre-potential or spontaneous gradual depolarization:

a. At start, membrane potential is -60 mV → special slow Na^+ channels open → inward (depolarizing) "**funny" current** (I_f) → spontaneous depolarization
b. At membrane potential -50 mV → transient **T-type Ca^{++} channels** open → inward Ca^{++} current (I_{CaT}) with electrochemical gradient → -40 mV.

Phase 0: At – 40 mV (firing level) 2 events occur at same time:

a. Closure of "funny" current (I_f) & transient Ca^{++} current (I_{CaT}) channels
b. Opening of **long-lasting L-type Ca^{++} channels** → more Ca^{++} entry (I_{CaL}) but not rapid → slow depolarization →"**slow response** AP"
c. Depolarization → gradual opening of delayed rectifying K^+ channels

Phase 3: repolarization phase (2 events occurr at same time):

a. Opening of **delayed rectifying K^+ channels** → outward K^+ current (I_k) along its electrochemical gradient → repolarization
b. Closure of LCa^{++} channels → stops inward depolarizing Ca^{++} currents (I_{CaL}).
c. Repolarization continues until -60 mV → gradual inactivation of outward K^+ current (I_k), & activation of funny current (I_f) → spontaneous new phase 4 ......

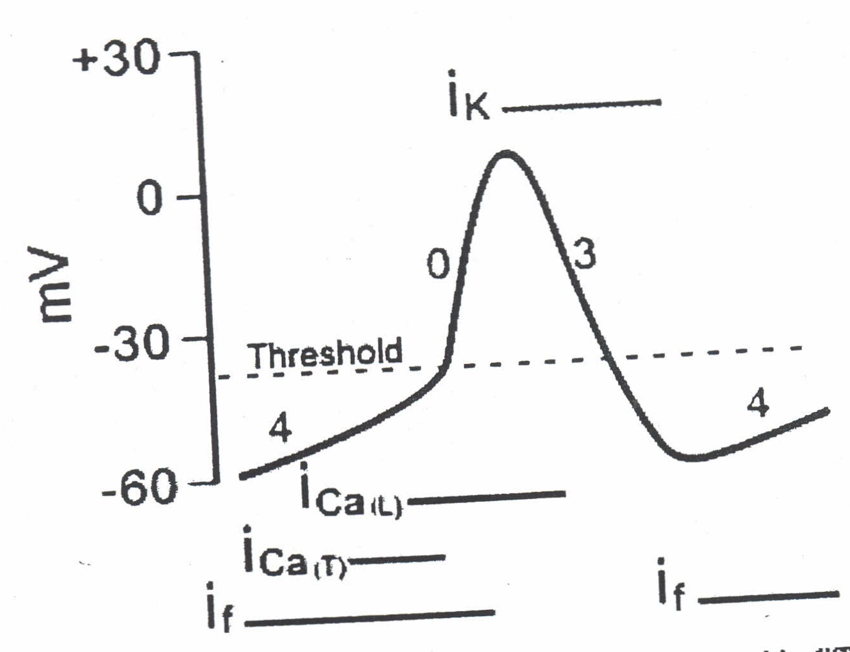
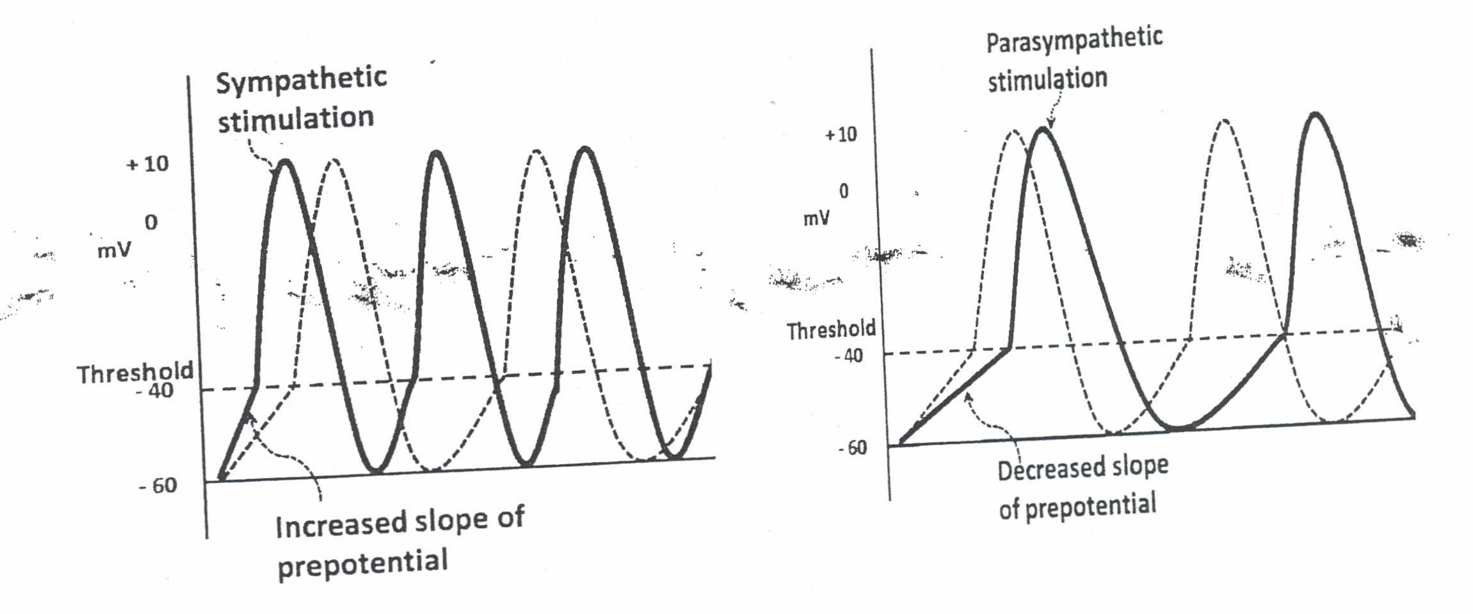


Figure (6): Pacemaker Action Potential with different ionic currents responsible for its phases.



Factors that affect the rate of discharge of SA node:

1- **Body Temperature:** +++ t° (fever) → +++ HR (tachycardia). +++1° → +++10 b/min

2- **Autonomic nerves activity:**

Sympathetic activity	Parasympathetic (vagal) activity
+++ discharge rate of SAN & HR (***tachycardia***)→ **positive chronotropy**	--- discharge rate of SAN & HR (***bradycardia***) → **negative chronotropy**
Mechanism:	Mechanism:
**Sympathetic→ Norepinephrine → β_1-adrenoreceptors → +++ c-AMP → +++ funny current → +++ slope of phase 4 → reach phase 0 more rapid	**Vagus → Acetylcholine → muscarinic receptors → ---- c-AMP → ---- funny current → ---- slope of phase 4 → reach phase 0 in a longer time **Acetylcholine → +++ K^+ channels (K_{Ach}) → K^+ efflux → opposes the funny current & --- the slope of phase 4 more & more

3- **Catecholamines:** Adrenal medulla → epinephrine & norepinephrine → +++HR

4- **Extracellular K^+ level:**

a. **Hypokalemia**→ tachycardia

b. **Hyperkalemia** → bradycardia

5- **Ca^{++} channel blockers** → inactivation of L-type Ca^{++} channels → bradycardia

II- Conduction of Action Potentials within the heart

Spread of AP between cardiac cells occurs through **gap junctions** → direct electric conduction (Low electric resistance → rapid transmission)

The velocity of conduction between cells depends on:

1- **Electrical resistance between cells**: The more the n= of gap junctions at intercalated discs → the faster the conduction.

Hypoxia or +++ intracellular free Ca^{++} → ----- conduction through gap junctions

2- **Amplitude & speed of AP upstroke**:

Slow upstroke in SAN & AVN → slow conduction

Initiation & propagation of cardiac impulse

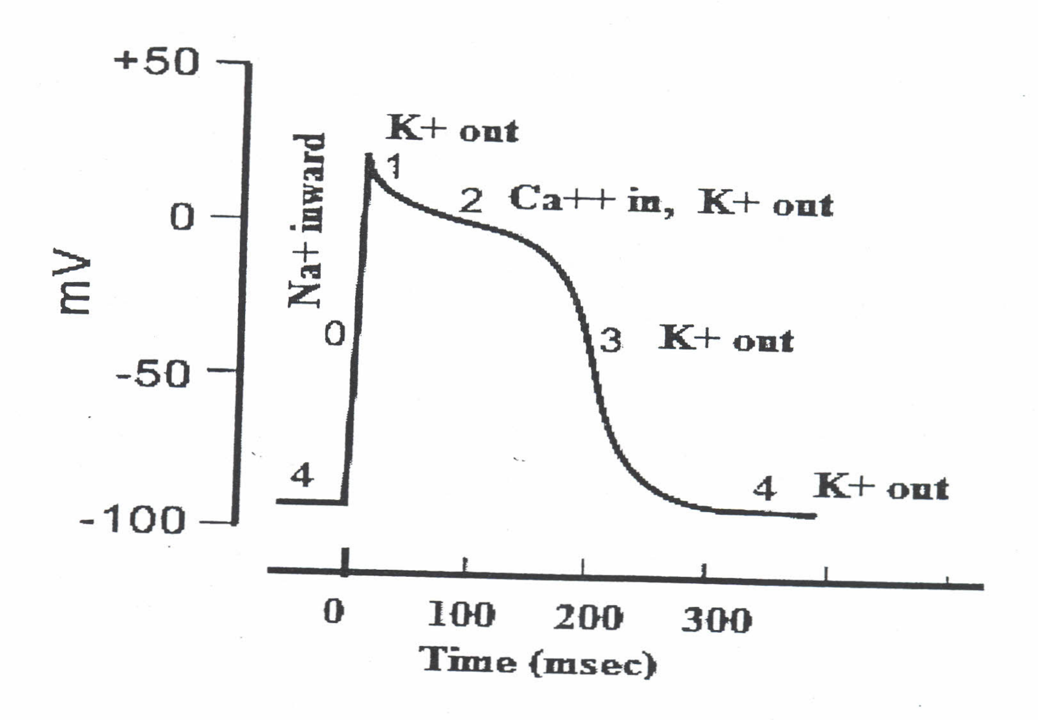
1. AP generated at SA node → **atrial myocytes (0.5 m/sec).**

Internodal bundles transmit AP directly from SA node to AV node **(1 m/sec).**

2. AV node → only pathway for transmission of AP from atria to ventricles

Conduction within the AV node is slow (0.05 m/sec) due to:

a- Few gap junctions   b- Slow upstroke of the AP



+50
0
-50
-100
mV
Na+ inward
K+ out
1
2 Ca++ in, K+ out
0
3 K+ out
4
4 K+ out
0
100
200
300
Time (msec)

Importance of slow conduction within AV node:

- Delays arrival of AP from atria to ventricles for 0.1 sec → gives atria enough time to contract & fill the ventricles before they contract
- Limits the rapid frequency of impulses from atria to ventricles in some diseases

3. AP from AV node → **bundle of His** → left & right **bundle branches** → **Purkinje fibers** (very rapid **4 m/sec** from subendocardium (in) to epicardium (out)) → AP reach all cells at same time → effective pumping
4. AP can spread from one **ventricular myocytes** to another at **0.5 m/sec**
5. **Factors affecting the rate of conduction:**
   - +++Sympathetic → β_1 adrenergic receptors → +++ ionic conductance → faster AP upstroke → +++ rate of conduction
   - +++Parasympathetic → muscarinic receptors → --- ionic conductance → slower AP upstroke → --- rate of conduction
   - Digitalis → +++ parasympathetic activity → ---- conduction velocity

III- Cardiac Myocyte (Non-pacemaker)Action potential

Rapid depolarization from RMP (-90 mV) to firing level (-65 mV) by cell-to-cell conduction of depolarizing potential; **Cardiac AP is then generated:**

Phase 4 = RMP

- continues till cardiac cells become depolarized
- K^+ slowly moves out (I_{k1}) through **inward rectifying potassium channels.**

Phase 0 = depolarization

- rapid upstroke of AP from resting value to +20 mV
- influx of Na^+ through **fast Na^+-channels** → inward depolarizing current (I_{Na})
- --- K^+ conductance due to inactivation of inward rectifying K^+ channels
- Fast Na channels are inactivated (fast upstroke) → **"fast response AP"**.

Phase 1 = rapid small initial repolarization

- inactivation of fast Na^+ channels
- efflux of K^+ through **transient outward K^+ channels** → transient outward repolarizing current (I_{to})

Phase 2 = plateau

Membrane repolarization slows down → sustained around zero mV for 200 msec due to a balance between:

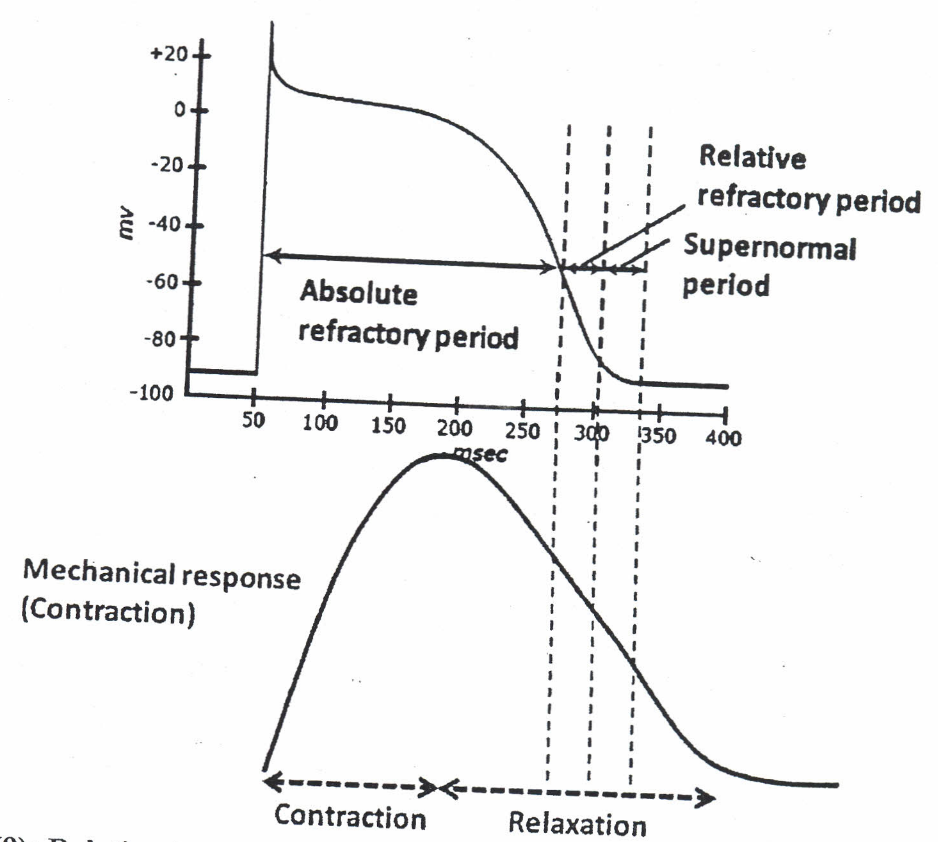


Figure (9): Relation between ventricular action potential and mechanical response (contraction).

- Inward positive current:

  Inward Ca^{++} current, through **long lasting Ca^{++} channels (I_{CaL}).

  - Channels start to open at -40 mV in phase 0 → fully active in phase2
  - Remain open for long time → spontaneous inactivation = time-dependent

  ** +++Na^+-Ca^{++} exchanger activity near the end of plateau (due to +++ $Ca^{++}i$) → 1Ca^{++} out & 3 Na^+ in (net → 1 +ve ion influx) → prolongs the plateau

- Outward positive K^+ current through **delayed rectifier K^+ channels (I_k)**

Phase 3 = rapid repolarization

- long lasting Ca^{++} channels closed
- **delayed rectifier K^+ channels** → maximally active → outward K^+ current (I_k) → repolarization (-80 to -85 mV) → gradual closure of delayed rectifier K^+ channels
- **inward rectifying K^+ channels** → gradually open → outward repolarizing current (I_{k1}) → complete repolarization to RMP (-90 mV)

Relationship between AP & contraction in cardiac myocyte

- Contraction → starts just after beginning of AP → reaches maximum at end of plateau (phase 2).
- Repolarization (phase 3) → coincides with 1st half of relaxation.

Excitability changes during action potential

1- **Absolute refractory period ARP:**

- Phases 0, 1, 2 & part of 3 → zero excitability (all Na channels are opened in phase 0 & inactivation gates are closed in phases 1 & 2)
- ARP → occupies contraction & early relaxation → prevent tetanic contractions

2- **Relative refractory period RRP:**

Phase 3 of AP → supra-threshold stimulus can elicit a new AP

3- **Supernormal period (vulnerable period):**

Late part of phase3 → can respond to a weaker stimulus → arrhythmias

Mechanical Properties of Cardiac Muscle

Excitation contraction coupling

1- Membrane depolarization → open L-type Ca^{++} channels → Ca^{++} enter → +++ Ca^{++} below sarcolemma → open "ryanodine- Ca^{++} release channel" in terminal cisterns of SR → +++ Ca^{++} release from SR (**"Calcium-induced Calcium release"**).

2- Ca^{++} binds to Troponin-C → contraction as described for skeletal muscle

3- Ca^{++} release decreases when AP ends.

4- **Relaxation: Ca⁺⁺ is removed from the cytoplasm by:**

a. Ca^{++} pump into SR (sarco-endoplasmic reticulum calcium ATPase, "SERCA")

b. Ca^{++} is transported into ECF by:

- Na^+-Ca^{++} exchanger
- Ca^{++} pump

Ca^{++} → determines the force of contraction (**contractility** or **inotropic state**).

Ca^{++} release during rest is not maximal. More Ca^{++} release → +++contractility/+++force (**+ve inotropic**). Less Ca^{++} release → ----contractility/----force (**–ve inotropic**)

Regulation of Contractility (inotropic state) of cardiac myocytes

Positive inotropic mechanisms	Negative Inotropic Mechanisms
1- +++ sympathetic or catecholamines → +++β-adrenergic receptors → +++ c-AMP→ activates Protein Kinase A (PKA)→ +++ Ca^{++} in cells: a. PKA phosphorylates L-Ca^{++} channel →open for longer time→ enter more Ca^{++} b. PKA phosphorylates certain sites on SR → more Ca^{++} release 2- Glucagon → +++ c-AMP in myocytes 3- +++ECF-Ca^{++} concentration→ +++Ca^{++} entry 4- Drugs: a. Digitalis → inhibits Na^+-K^+ ATPase → +++ Na^+ in → +++ Na^+-Ca^{++} exchanger → moves Na^+ out & Ca^{++} in→ +++ Ca^{++} in b. Xanthines (caffeine) → ---- c-AMP breakdown → +++ c-AMP in myocytes	1- Ischemia to cardiac muscle (---blood supply) → hypoxia→ ----ATP energy for contraction 2- +++ parasympathetic (vagus) →acetylcholine → +++ muscarinic M2 receptors → ---c-AMP 3- Adenosine → ----c-AMP production 4- Drugs: a. Ca^{++} channel blockers (dihydro-pyridine) → inhibit L-Ca^{++} channels→ ----Ca^{++} entry b. Anesthetic drugs.

Regulation of Myocyte Relaxation (lusitropy)

1- +++β-adrenergic receptors → +++ c-AMP & PKA → accelerate relaxation by:

a. Activation of SERCA pump → rapid removal of Ca^{++} by SR → rapid relaxation

b. Decreased binding of Troponin to Ca^{++}.

2- Myocardial ischemia inhibits relaxation (+++Ca^{++}permeability → ++++++ Ca^{++} in → inhibits relaxation (weak contraction & poor relaxation)

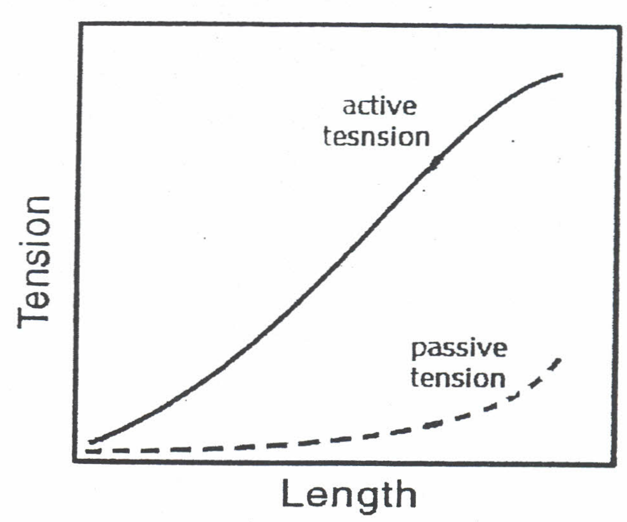


Figure (39): Passive and active length-tension relationships.

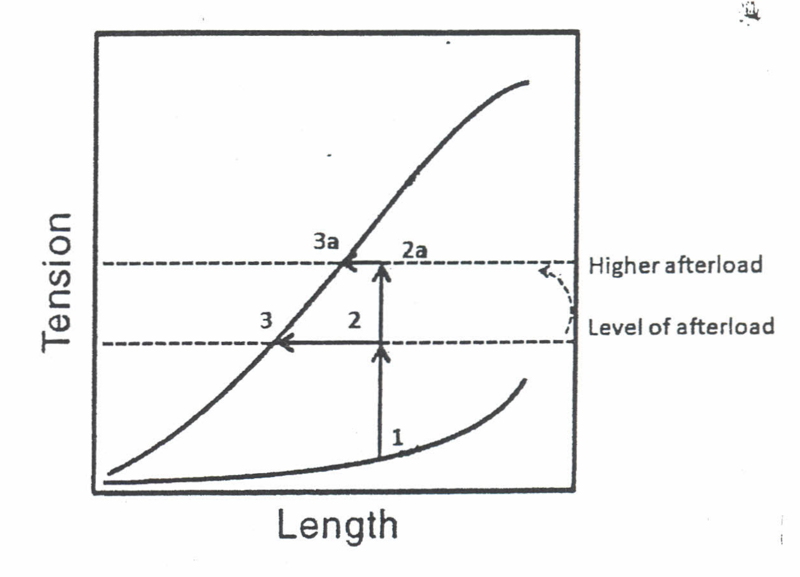


Figure (41): Effect of increasing afterload on cardiac muscle shortening.

Isometric and Isotonic contraction of isolated cardiac muscle

Isometric Contraction	Isotonic contraction
• Isolated cardiac muscle → fixed to holder & attach a heavy load to its lower end. • Load stretches the muscle to certain degree; • Stimulate the muscle → contracts →maximum tension → but not able to shorten (heavy load) • Sarcomeres are shortened→ stretch of elastic elements • +++ the tension in muscle to maximum while its length remains constant	• Same muscle but using small load • Muscle is stretched to same degree; • Stimulate the muscle → contraction starts isometric → +++ muscle tension till = load • Muscle shortens & lift the load • Tension remains constant

What is meant by "*preload*" and "*afterload*"?

Preload → degree of stretching of cardiac muscle before it contracts

Afterload → load against which the muscle contracts: load lifted by the muscle;

- isotonic contraction → if the muscle succeeds to lift the load;
- isometric contraction → if the muscle could not lift the load

Length-Tension Relationship in Cardiac Muscle

a. Passive length-tension relationship:

Passive stretch of cardiac muscle → +++ tension within the muscle

b. Active length-tension relationship: **Frank-Starling Law:-**

Within limits, tension developed during isometric contraction is directly proportional to the degree of stretching of the muscle (i.e. preload).

Performance of Cardiac Muscle

Indicators of performance:

1- Degree of shortening: (length-tension diagram)

2- Velocity of shortening: (load-velocity relationship)

1- Effect of changing afterload on cardiac muscle performance

a- Effect of changes in afterload on muscle shortening:

- +++ afterload → ---- degree of shortening (inverse relationship)
- The muscle starts isometric contraction at same preload (1).
- +++ tension to be equal to the new higher afterload (2a).
- Contraction becomes isotonic & muscle shortens (3a).
- Degree of shortening is smaller (distance between 2a & 3a).

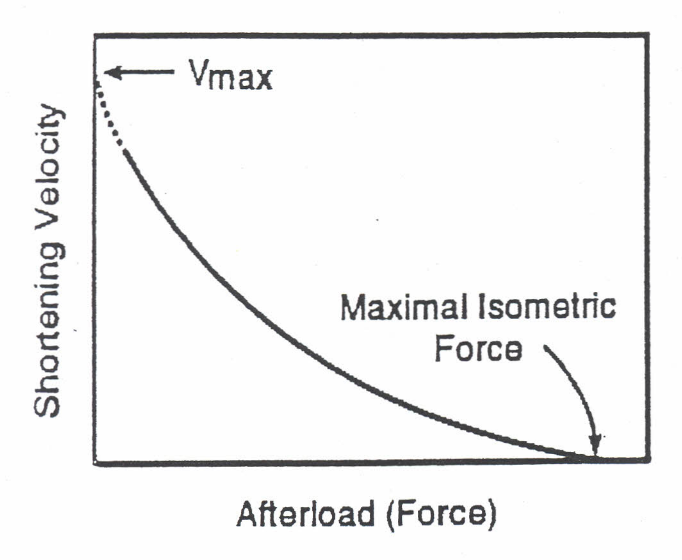


Figure (42): Effect of increasing afterload on velocity of shortening of cardiac muscle.

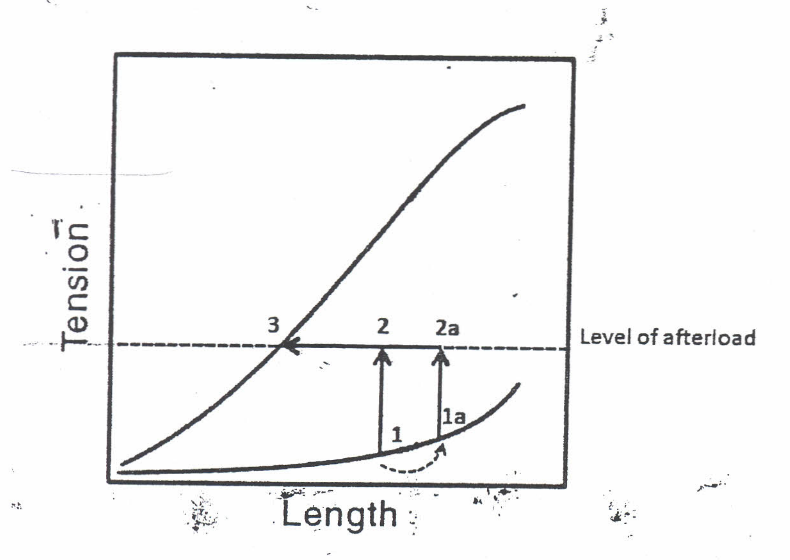


Figure (43): Effect of increasing preload on cardiac muscle shortening.

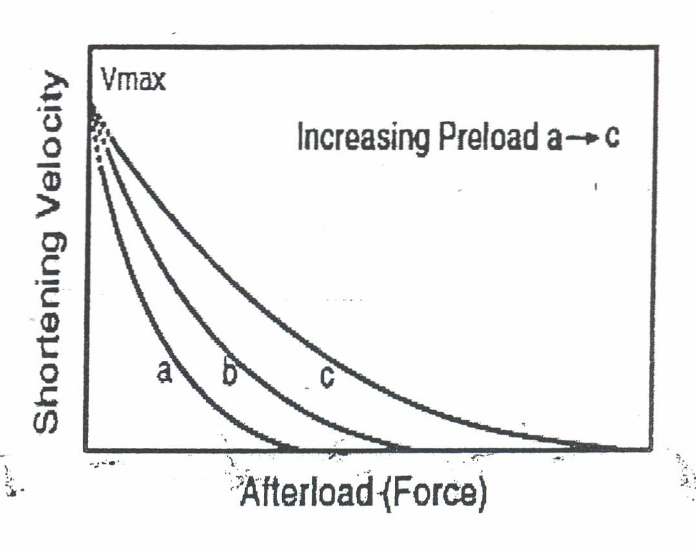


Figure (44): Effect of increasing preload on velocity of shortening of cardiac muscle.

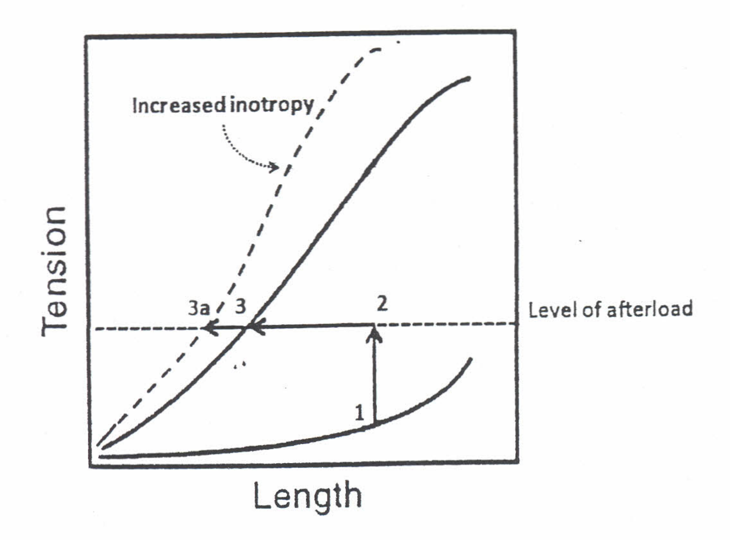


Figure (45): Effect of increased inotropy on degree of shortening of cardiac muscle.

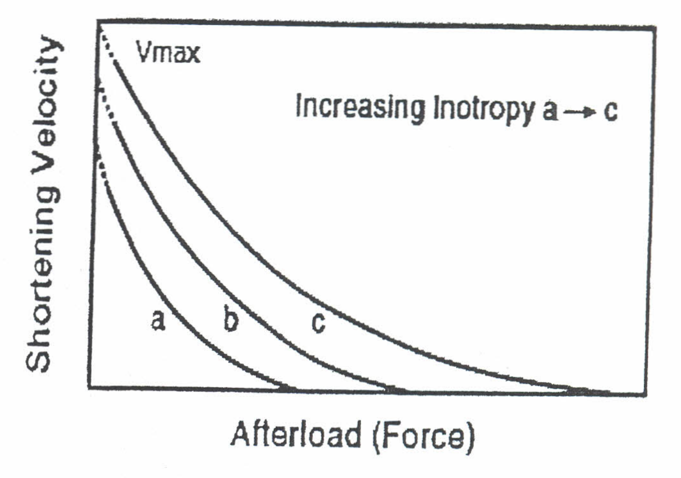


Figure (46): Effect of increased inotropy on the velocity of shortening of cardiac muscle.

b- **Effect of changes in afterload on velocity of shortening:**

- +++ afterload → ---- velocity of shortening (inverse relationship)
- Zero Velocity of shortening → when load ≥ maximum isometric tension
- Maximal velocity of shortening (V_{max}) → when load = zero (extrapolation) (muscle can't contract against zero load))

2- Effect of changing preload on cardiac muscle performance

a- **Effect of changes in preload on muscle shortening:**

- +++ preload → +++ degree of shortening (directly proportional)
- +++ preload → stretch the muscle to higher length (1a)
- Muscle contracts isometrically to the same level of afterload (2a)
- Then muscle contracts isotonically (3)
- Degree of shortening is greater (distance between 2a & 3)

b- **Effect of changes in preload on velocity of shortening:**

- +++ preload → +++ velocity of shortening (V_{max} is not changed)
- +++ preload shifts load-velocity curve up & right

3. Effect of changing inotropic state on cardiac muscle performance

a- **Effect of changes in inotropic state on muscle shortening:**

- +ve inotropics → shifts length-tension relationship up & left (+++ shortening)
- −ve inotropics→ shifts length-tension relationship down & right (--- shortening)

b- **Effect of changes in inotropic state on velocity of shortening:**

- +ve inotropics → shifts load-velocity curve up & right (faster contraction)
- +++V_{max} (changed only by +ve inotropics); thus V_{max} → index of contractility
- −ve inotropics → the opposite occurs

1. Effect of changing frequency of stimulation on force of contractions

+++ frequency → gradual +++ in force of contractions (inotropy) → **"staircase phenomenon" / "treppe"** : rapid repetition of contractions → no enough time for complete removal of released Ca^{++} → +++ Ca^{++} in cytoplasm &+++ force of contraction

Cardiac Cycle (systole & diastole)

Ventricular systole: 2,3,4

Ventricular diastole: 5,6,7,8,1

Early diastole: 5,6 Mid- diastole:7,8 Late diastole: 1

Phase	1: Atrial Systole	2: Isovolumetric Contraction	3: Rapid Ejection	4: Reduced Ejection
Time	(0.1 sec)	(0.05 sec)	(0.15 sec)	(0.1 sec)
ECG	Initiated by P wave	Starts by QRS		start of "T" wave
Atrial pressure	+++ → ("a" wave) • Limited backflow of blood into vena cavae (contraction of atria → narrow orifices of veins) • Atrial contraction → 30% of ventricular filling during rest; (shares more during exercise)	Small +++ → ("c" wave) (bulging of cusps inside the atria }	sharp small - - - due to pulling of cusps downward	+++ due to accumulation of venous blood in atria → "v" wave
Ventricular pressure	+++ (left → 9mmHg; right → 4mmHg)	+++ (Left → 80mmHg; right → 10mmHg)	+++ (left → 120mmHg; right → 25mmHg)	- - - - & finally becomes lower than arterial pressure;
Ventricular volume	+++ → end-diastolic volume "EDV" (130 ml).	Constant	----- rapidly due to blood ejection	---- slowly End-systolic volume "ESV" = (60 ml) Stroke volume "SV" = (70 ml) EDV - ESV = SV (130ml - 60ml)
AV valves	opened	Closed (ventricular pressure > atrial pressure	Closed due to high ventricular pressure	Closed (ventricular pressure> atrial pressure
Semilunar valves	Closed (as Ventricular pressure < arterial pressure)	Closed (ventricular pressure < arterial pressure)	Opened → blood ejection	
Heart sounds	4th HS ..."S_4"	1st HS... "S_1" (Closure of AV valves)		

aortic & pulmonary pressures	Gradual decrease (blood leave them peripherally)	---- → 80mmHg in aorta & 10mmHg in pulmonary	+++ → aorta:120mmHg; pulmonary: 25mmHg	---- but > than ventricular pressure Ejection continues due to momentum of ejected blood

Phase	5: Protodiastolic	6: Isovolumetric Relaxation	7: Rapid Filling	8: Reduced Filling
Time	(0.04 sec)	0.06 sec	0.1 sec	0.2 sec
Atrial pressure	Period between the end of ventricular contraction & closure of semilunar valves Blood tends to flow back into the ventricles but prevented by closure of semilunar valves	+++Atrial pressure due to +++ venous blood ("v" wave)	----Atrial pressure rapidly due to rapid flow of blood out of them	Small decrease
Ventricular pressure		rapid drop in ventricular pressure to below arterial pressure	--- Ventricular pressure in spite of filling; because they relax during early filling.	+++Ventricular pressure as they fill with blood.
Ventricular volume		Constant (A-V & semilunar valves are closed)	+++ rapidly due to rapid filling by pressure gradient → passive filling (70% during rest	+++ slowly due to slower filling
AV valves		Closed Ventricular pressure > atrial pressure	opened ventricular pressure < atrial pressure	
Semilunar valves		closed	closed	Closed
Heart sounds		Sudden closure of semilunar valves → "2nd HS ....S_2".	"3rd HS ..... S_3".	
aortic & pulmonary pressures		---- Arterial pressure gradually due to flow of blood to peripheral vessels	----Arterial pressure as blood flows to the periphery	Arterial pressure continues to decrease

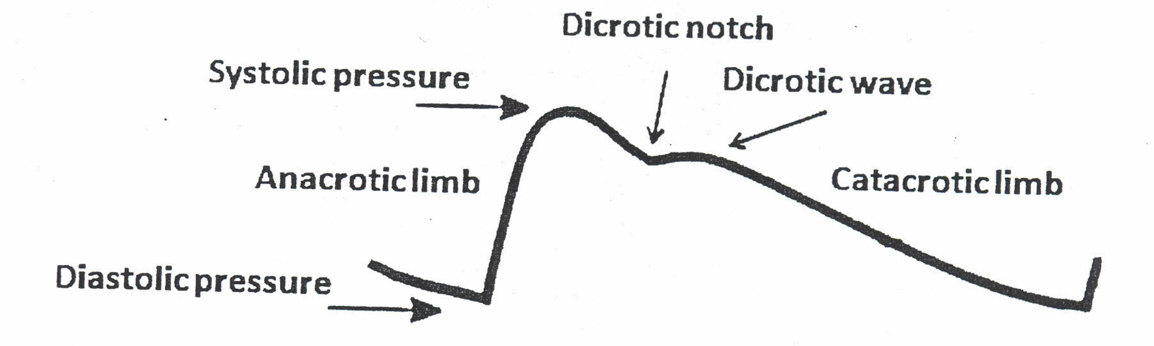


Figure (50): Aortic pressure curve.

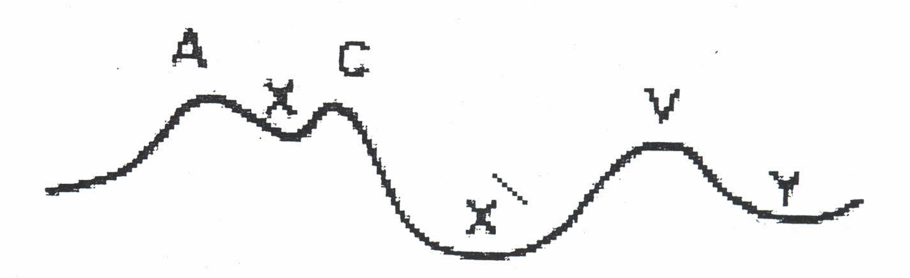
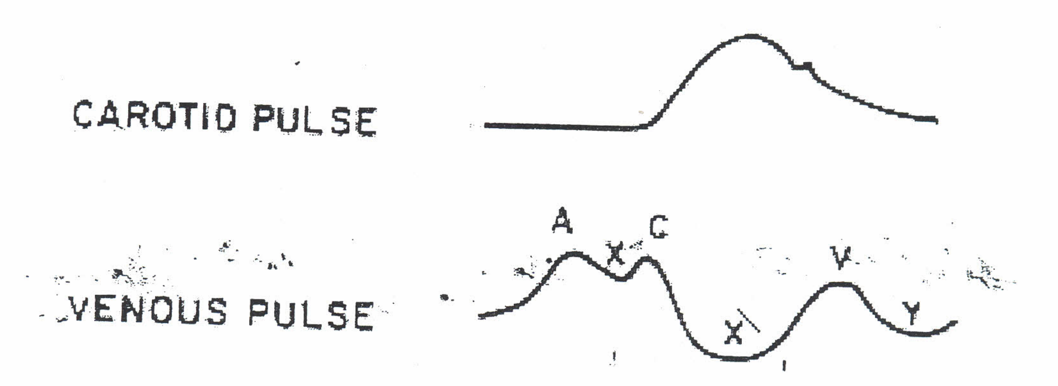


Figure (51): Jugular venous pulse curve.



Aortic Pressure Curve= aortic pressure changes during cardiac cycle

Ascending limb "anacrotic limb":

It coincides with maximal ejection phase.

+++Aortic pressure to maximum (120mmHg)→ **systolic arterial blood pressure**

Descending limb "catacrotic limb":

It coincides with the rest of cardiac cycle

----Aortic pressure to minimum (80mmHg)→ **diastolic arterial blood pressure**

The following is observed on the catacrotic limb:

- Dicrotic notch, due to sudden closure of aortic valve at the end of systole.
- Dicrotic wave, due to elastic recoil of aorta → +++ aortic pressure

Right Atrial Pressure Curve and the "Jugular Venous Pulse JVP"

- No valves exist between the right atrium & superior & inferior vena cava.
- Pressure changes occurring in right atrium during cardiac cycle are transmitted to these veins & Jugular vein:

1. "a" positive wave: → atrial contraction
2. "x" negative wave: → atrial relaxation
3. "c" positive wave: → bulging of tricuspid valve inside the right atrium during isovolumetric contraction phase
4. "x\" negative wave: → downward pull of A-V ring by ventricular contraction during rapid ejection phase
5. "v" positive wave: → accumulation of venous return in right atrium while the tricuspid valve is closed
6. "y" negative wave: is due to flow of blood out of the right atrium after opening of tricuspid valve during ventricular filling phase

Relationship between JVP & carotid pulse:

- "x\" negative wave occurs with carotid pulse → jugular veins collapse normally with carotid pulsation
- "v" wave occurs with descending limb of carotid pulse (with collapsing carotid pulse)

Ventricular pressure-volume relationship: Pressure-Volume Loop:

The relationship between degree of stretch of cardiac muscle & developed tension in isolated cardiac muscle → can be applied to the ventricle with these **modifications:**

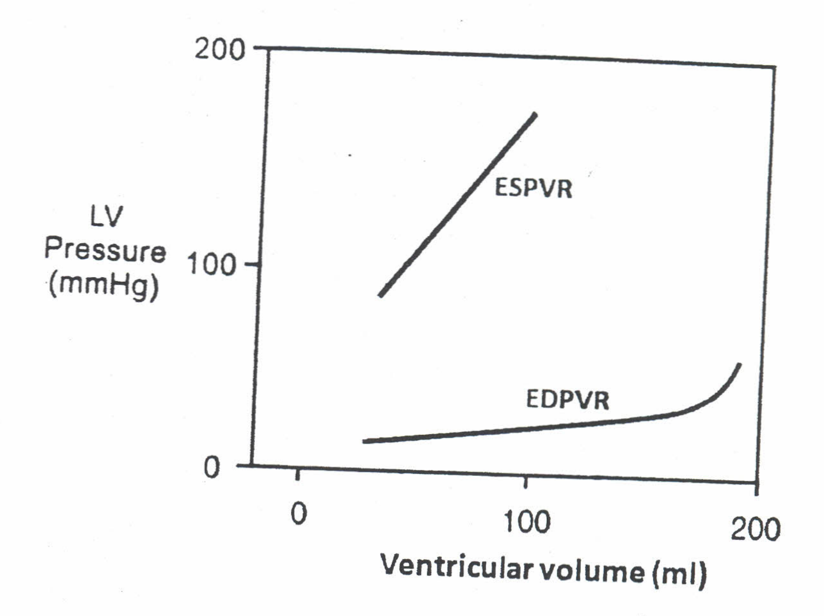


Figure (53): End-diastolic and end-systolic pressure-volume relationship.

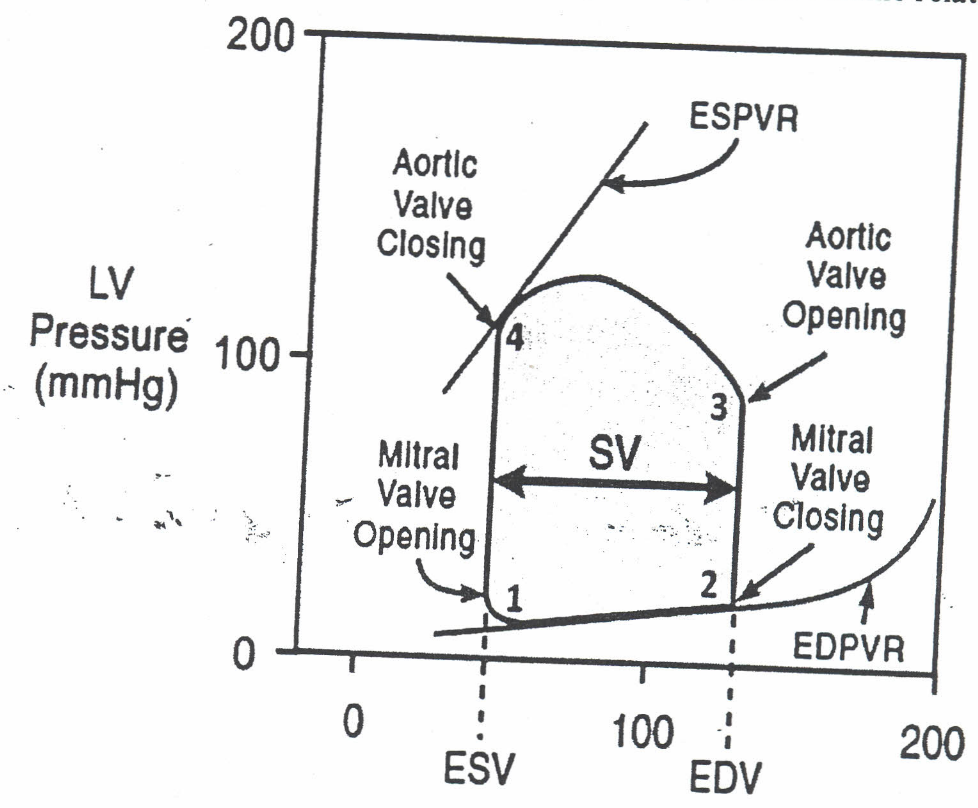


Figure (54): Left Ventricular Pressure-Volume loop.

length-tension relationship for isolated cardiac muscle	**Pressure-Volume loop of whole heart**
Degree of stretch	**volume of ventricle at end of diastole (EDV**
tension	**intraventricular pressure**
passive length-tension relationship	**"end-diastolic pressure-volume relationship EDPVR"**
Tension developed during isometric contraction	**maximal pressure developed in ventricle during contraction while the aorta is clamped ("end-systolic pressure" ESP)= isometric contraction**
active length-tension relationship	**"end-systolic pressure-volume relationship ESPVR"**

<u>NB:</u> Slope of the ESPVR depends on inotropic state of ventricular muscle.

a. +ve inotropics → +++ the slope of ESPVR (shifts the ESPVR up & left)
b. -ve inotropics have an opposite effect

<u>Pressure-volume loop during a complete cardiac cycle: changes in ventricular pressure in relation to changes in ventricular volume</u>

1. At beginning of diastole, ventricular volume = "end-systolic volume ESV" (1)
2. Ventricle fills with blood → +++pressure till the "EDV" (2). Line "1-2" → ventricular filling phase
3. Ventricle contracts isometrically (2) → mitral valve closes → 1st HS & +++ ventricular pressure (3). Line "2-3" → isometric contraction phase
4. At "3", intraventricular pressure > aortic pressure → aortic valve opens
5. Ejection of blood starts → ---- ventricular volume but +++ ventricular pressure to maximum then ---- again → end of systole ("4"). Line "3-4" → ejection phase
6. At end of systole → Intraventricular pressure = ESP ("4" on ESPVR)
   → Ventricular volume = ESV
7. Ventricular relaxation starts → ----Ventricular pressure < aortic pressure → aortic valve closes → 2nd HS (at "4").
8. Isometric relaxation continues till intraventricular pressure < atrial pressure → mitral valve open ("1"). Line "4-1" → isometric relaxation phase
9. Now, the ventricle starts to fill and a new cycle starts.
10. **Width** of the pressure volume loop → **stroke volume (SV)**

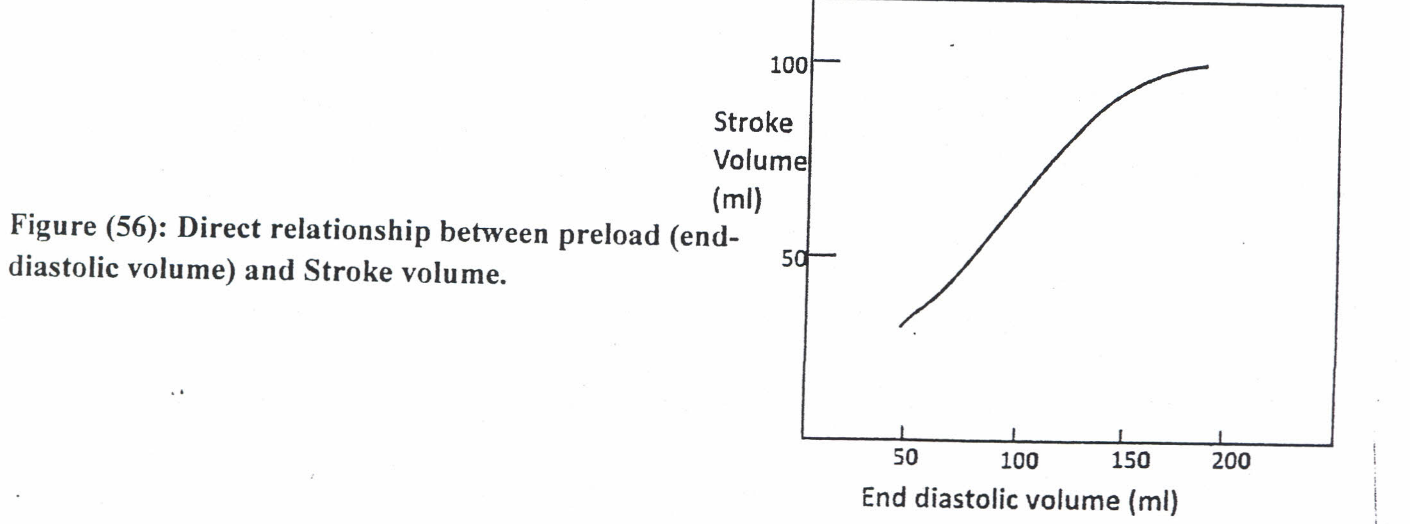


Figure (56): Direct relationship between preload (end-diastolic volume) and Stroke volume.

Cardiac Output

Cardiac output (CO): volume of blood pumped by each ventricle/minute (5 L/min)

Cardiac Index (CI): CI = CO (L/min) ÷ by body surface area (m^2) = 3.2 L/min/m^2

Cardiac output increases in	Cardiac output decreases in
1- Physical exercise (up to 700%). 2- Anxiety and excitement (up to 100%). 3- After meals (30%). 4- High environmental temperature. 5- Pregnancy.	1- Standing from supine position (30%) 2- Rapid cardiac arrhythmias and many other heart diseases.

Determinants of Cardiac output: Heart rate & Stroke volume

CO = **stroke volume (SV)** x **heart rate (HR)**

Stroke volume = volume of blood ejected by each ventricle each heart beat

Heart rate = number of beats per minute

Control of Cardiac Output

I- Effect of changes in heart rate on cardiac output

- Changes in HR are quantitatively more important than changes in SV.
- +++HR during exercise 100-200% while +++ SV by 50% in untrained person
- HR is controlled mainly by autonomic nerves & some other factors
- +++ HR alone from 70-140 beat/min → no change in CO (because of ----- ventricular filling → -----SV → thus no change in CO)
- +++ HR alone above 150/min → ---- CO (marked ---- in SV can't be compensated by the +++ in HR)
- ---- HR alone below 60/min → ---- CO (marked ---- in HR can't be compensated by the +++ in SV)
- During muscular exercise, +++ HR (doubled) → +++ CO (more than double) because of the associated +++ in SV (+++sympathetic)

II- Regulation of Stroke Volume

1- Effect of changes in preload on stroke volume

- Preload = degree of stretch of cardiac myocytes before they start to contract (at end of diastole); measured by the sarcomere length
- EDV → index of sarcomere length (index of preload)
- **EDV depends on venous return (VR);** +++ VR → +++ EDV & the preload

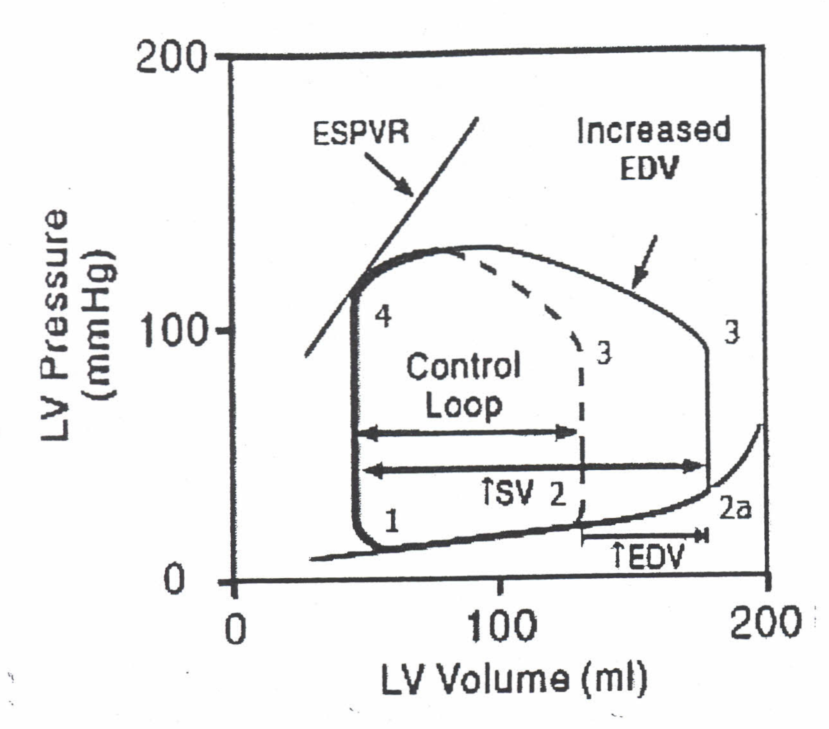


Figure (57): Effect of increasing preload (EDV) on pressure-volume loop, showing increased stroke volume (dashed-line loop is control loop before increasing EDV)

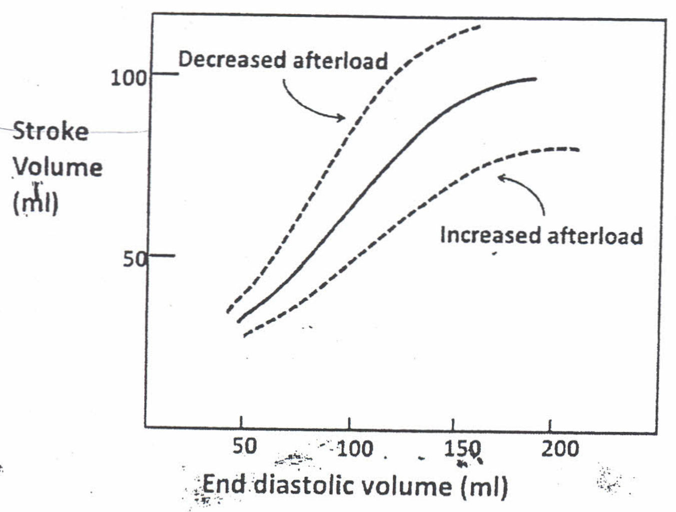


Figure (58): Effect of changing afterload on stroke volume.

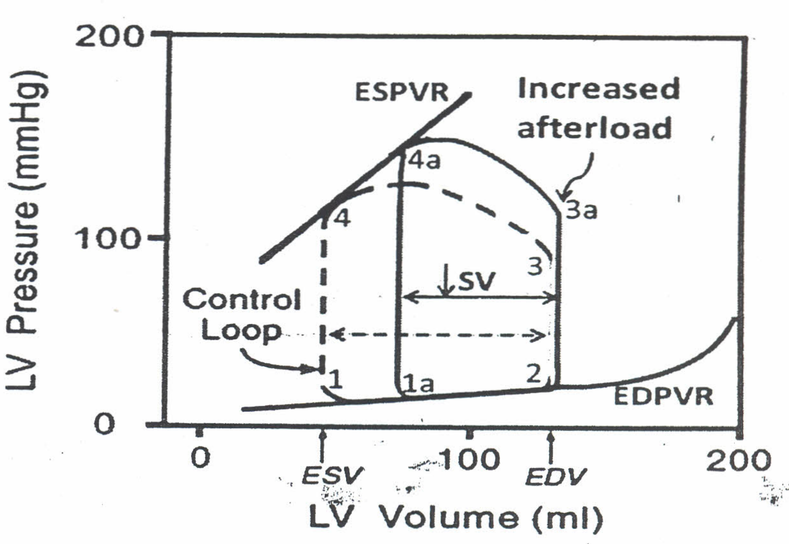


Figure (56a): Effect of sudden increase in afterload on pressure-volume loop, showing decreased stroke volume.

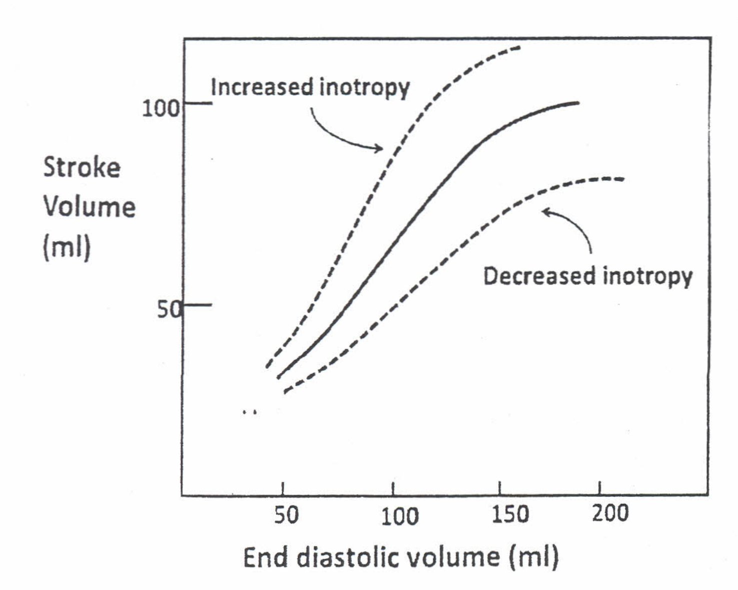


Figure (60): Effect of changing inotropy on stroke volume.

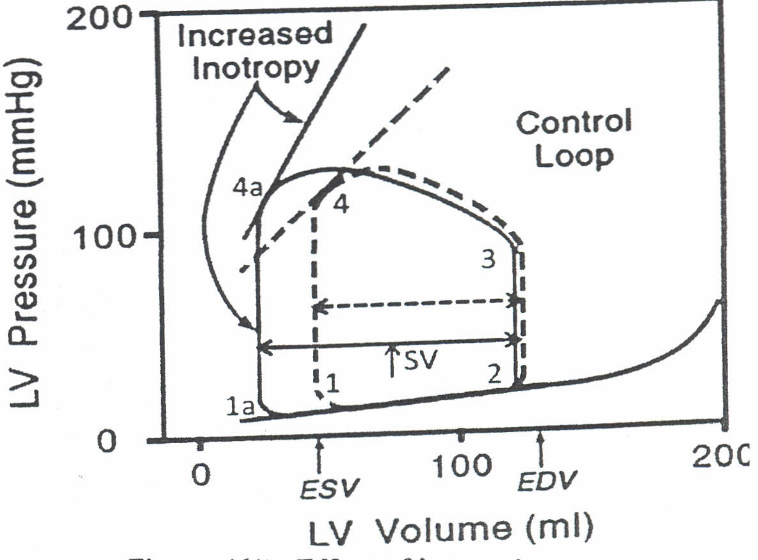


Figure (61): Effect of increasing inotropy on pressure-volume loop showing increased SV

- **+++ preload → +++ SV** (Frank-Starling's law) → **"heterometric autoregulatory mechanism"** (matches SV & CO with VR)
- **Using the ventricular pressure-volume loop:**
  a. More ventricular filling (+++ preload) → higher EDV (2a)
  b. Isometric contraction starts at (2a) till the same ventricular pressure (3) → aortic valve opens → Ejection starts till the end-systolic pressure (4) → aortic valve closes → Isometric relaxation occurs at same ESV (1)
  c. +++ width of pressure-volume loop → +++ SV
  d. +++ preload → +++ degree of shortening & +++ velocity of shortening → +++ SV
- **Several factors can affect ventricular preload:**
  1. +++ venous pressure & VR → +++ ventricular filling→ +++ preload
  2. Strong atrial contraction → +++ preload.
  3. +++ HR (with constant VR) → ---- preload (no enough time for ventricular filling)
  4. ---- ventricular compliance (hypertrophy or myocardial infarction) → ---- preload

2- Effect of Afterload on Stroke Volume

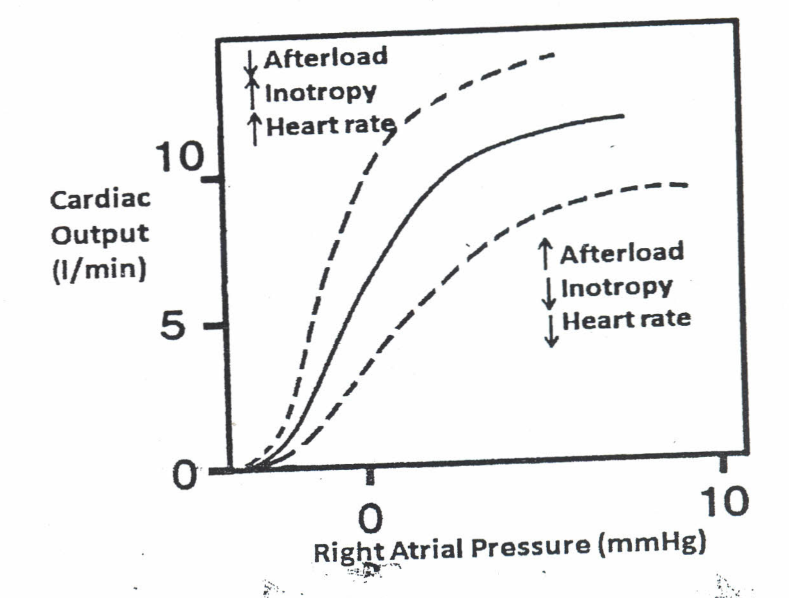
Afterload = load against which the ventricle contracts to eject blood = aortic pressure

- **At constant preload, +++ afterload** → ---- SV (shifts the preload & SV relation-ship downwards) (---- afterload has an opposite effect → shifts the curve upwards)
- **Using the ventricular pressure-volume loop:**
  a. At Same EDV (2), the ventricle starts isometric contraction → +++ ventricular pressure to higher level (3a) (new higher afterload) → aortic valve opens
  b. Ventricle ejection starts & ends at higher ESP (4a) & higher ESV (1a) → ----SV
  c. +++ afterload→ --- degree of shortening & --- velocity of shortening → ---- SV

3- Effect of Inotropic State on Stroke Volume

- **At constant preload & afterload, +++ inotropy** → +++ SV (shifts the preload & SV relation-ship upwards); ---- inotropy → shifts the curve downwards
- **Using the ventricular pressure-volume loop:**
  a. Isometric contraction starts at same EDV (2) & ends at same afterload level (3)
  b. Ejection continues till aortic valve closes (4a) on the shifted ESPVR line (up & left) by +++inotropy)
  c. Ejection continues to a lower ESV (1a) → +++SV (+++ inotropy → ---- ESV)
  d. +++ inotropic state → +++the degree & velocity of shortening → +++ SV

Figure (62): Cardiac function curve showing the effects of changing afterload, inotropy and heart rate.



Ejection fraction (EF)

- Fraction of the EDV that is ejected with each beat (normally >55% (or 0.55))
- EF is used clinically as index of contractility (+++ inotropy → +++ EF & vice versa)

$$\text{Ejection Fraction} = \frac{\text{Stroke Volume (SV)}}{\text{End Diastolic Volume (EDV}}$$

Cardiac Function Curve

- It describes the relationship between right atrial pressure (RAP) & cardiac output (CO)
- It is an expression of Starling's law: +++ RAP → +++ CO;
- RAP represents the preload (pressure that fills the ventricle to its EDV)
- **Heterometric autoregulation** → Intrinsic mechanism → +++ CO independent of any external nervous or hormonal stimulation
- It is limited → heart pumps 13 L/min (2.5 times the normal VR) without nervous or hormonal stimulation. Further +++ in RAP → no further +++ in CO (plateau)

++++ slope of the cardiac function curve	----- slope of the cardiac function curve
▪ +++ Heart rate (+++ sympathetic) ▪ +++ Inotropy (+++ sympathetic) ▪ ---- Afterload (VD & --- ABP). higher CO is achieved for same RAP; CO can exceed 13 L/min → "**hyper-effective heart**"	▪ ----- Heart rate (+++parasympathetic) ▪ ----- Inotropy (e.g. myocardial ischemia). ▪ ++++ Afterload (hypertension). lower CO is achieved for same RAP; maximum CO decreases below 13 L/min → "**hypo-effective heart**"

Cardiac Reserve CR

Maximum % +++ in CO achieved above normal in response to +++ body needs

- In normal young adult → CR = 300% - 400%; +++ CO from 5 L/min to 15-20 L/min (during maximal exercise)
- In well-trained athletes → +++ CR as high as 700% (35 l/min)
- In elderly people → ---- CR to 200% or even less
- In heart.failure → ---- CR down to zero%

Cardiac reserve depends on the following mechanisms:

1- **Heart rate reserve:** maximal HR during maximal exercise can be estimated by this equation: Maximal heart rate = 220 – age in years

= 200 beats/min in normal young adults

Normal resting HR = 75 /min; it can +++ from 75 to 200/min during exercise (HR reserve)

2- **Stroke volume reserve:** SV = 70 ml in normal young adults; it can +++ up to 200 ml during maximal exercise by:

a. +++ EDV (Frank-Starling's mechanism)

b. ---- ESV (by sympathetic stimulation or other +ve inotropic stimuli)

3- **Increased size of the heart (cardiac hypertrophy):**

a. **Eccentric hypertrophy "volume overload hypertrophy"**: in well-trained athletes who perform endurance exercise (prolonged moderate intensity exercise: long distance runners) → +++ heart mass by 50-60% & +++ ventricular EDV → enables the heart to pump greater SV

b. **Concentric hypertrophy "pressure overload hypertrophy"**: heart is exposed to prolonged high afterload (strength training) → +++ ventricular thickness with no +++ in ventricular volume → the ventricle can pump with greater strength without an +++ in wall stress. Then, ventricular compliance decreases (ventricle becomes stiffer) & ventricular filling may become deficient.